Kihara discloses phenyl derivatives of the indicated imidazoles, and a single unsubstituted thiophene derivative thereof. The above referenced proviso thus specifically excludes from all the pending claims compounds of the structure disclosed in Kihara, since both a phenyl group and a thiophene group are fully unsaturated 6 and 5 member rings structures, respectively.

Rejection of Claims 1-108 Pursuant to 35 USC §103(a)

The Examiner has again rejected claims 1-108 as allegedly obvious over Toyko (WO94-07866 or Orion (WO97-12874) or Zhang et al. Applicants respectfully traverse this rejection for the following reasons.

As stated in the last communication, the present invention is directed to compounds having a particular structure and which are selective agonists of the alpha 2_B and/or 2_B and 2_C adrenergic receptor subtypes. Thus, the claimed compounds are defined by structural and functional limitations, and the patentability of each of the rejected claims must be considered in light of all its limitations.

The Examiner has incorrect stated that "[a]pplicants must agree with the rejection to Zhang et al. since no arguments were presented as to why the patented subject matter is patentable over this reference." In fact, the argument on pages 7 and 8 of that Reply are addressed generally to the rejection in view of all (and each of) the references.

In repeating the rejection over the above-cited references, the Examiner has not addressed the points made on pages 7-10 of the Applicants' Reply, which is hereby incorporated by reference as part of this Reply. The Examiner has stated generally that the Applicants have not provided any showing of inobvious properties of the claimed molecules. Applicants respectfully submit this is not the case, and moreover, that the Examiner's Action fails to address each claim as a whole, including its functional limitations. The Examiner states that "[t]o be a viable reference the reference has to disclose structurally similar compounds which would render the claimed compounds structurally obvious and have a viable utility – this utility does not have to be the some [sic] utility applicants disclose for the claimed compounds." While Applicants have no opinion whether this rule might be true for a claim containing only structural limitations, it is decidedly untrue in the present case, in which each and every claim contains functional limitations.

[redacted]

As indicated in the prior Reply, the claimed molecules must be selective or specific for agonist activity at the alpha 2B and or the alpha 2C over the alpha 2A receptor. Despite the Examiner's assertions, Table 1, beginning on page 87, provides experimental evidence of the unexpected properties of the claimed compounds.

Finally, the Examiner has failed to provide any evidence, as he must in order to establish a *prima facie* case of obviousness, that the disclosed selective agonist activity was suggested by the prior art or that there existed motivation in the prior art to find the claimed set of compounds, limited as they are by this function.

CONCLUSION

For the above reasons Applicants believe the claims are now in condition for allowance, and respectfully request that the Examiner issue a Notice to that effect. No fee is thought to be required in connection with this communication. However, if Applicant is in error in this regard, please use Deposit Account 01-0885 for payment of any fee that may be due.

Respectfully Submitted,

Date: 5/2/02

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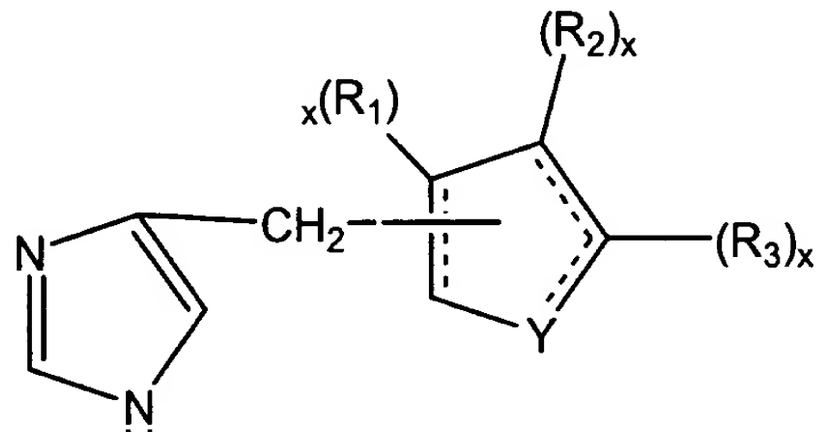
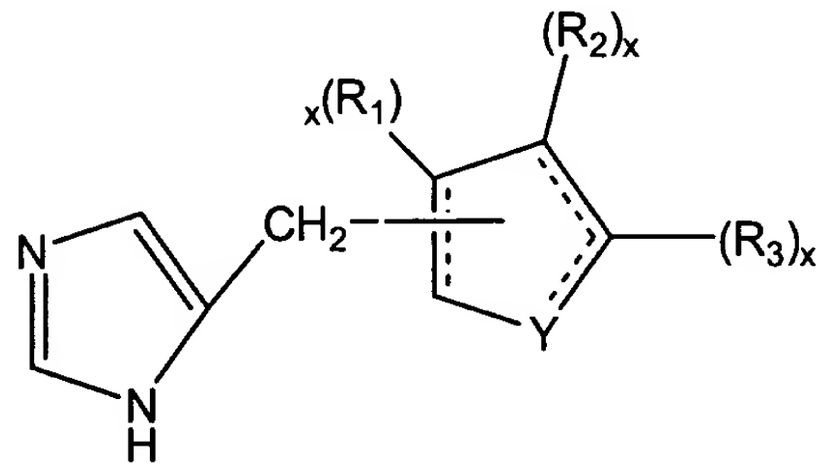
MARKED-UP VERSION OF THE AMENDMENTS

In the Claims:

13. (Twice Amended) A compound having a structure selected from the group consisting of:



and



in which each x is independently 1 or 2;

each R_1 is independently selected from the group consisting of H; halogen; C_{1-4} alkyl; C_{1-4} alkenyl; C_{1-4} alkynyl; --COR_4 where R_4 is H, C_{1-4} alkyl or C_{1-4} alkoxy; C_{3-6} cycloalkyl; aryl; heteroaryl; cyano; nitro; trihalomethyl; oxo; or $-(CH_2)_n$-X-$(CH_2)_m$-$(R_5)_o$ where X is O, S or N, n is 0-3, m is 0-3, o is 0-1, and R_5 is methyl or H_{1-2};

each R_2 and each R_3 are independently selected from the group consisting of H; halogen; C_{1-4} alkyl; C_{1-4} alkenyl; C_{1-4} alkynyl; --COR_4 where R_4 is H; C_{1-4} alkyl or C_{1-4} alkoxy; C_{3-6} cycloalkyl; aryl; heteroaryl; cyano; nitro; trihalomethyl; oxo; or $-(CH_2)_n$-X-$(CH_2)_m$-$(R_5)_o$ where X is O, S or N, n is 0-3, m is 0-3, o is 0-1, and R_5 is methyl or H_{1-2}; or an R_2 and an R_3 together <u>consist of</u> ~~comprise~~ a saturated, partly saturated, or unsaturated ring structure having the formula $-(C(R_6)_p)_q$-X_s-$(C(R_6)_p)_r$ $-X_t$—$(C(R_6)_p)_u$ where each R_6 is independently

selected from the group consisting of H; halogen; C_{1-4} alkyl; C_{1-4} alkenyl; C_{1-4} alkynyl; --COR_4 where R_4 is H, C_{1-4} alkyl or C_{1-4} alkoxy; C_{3-6} cycloalkyl; aryl; heteroaryl; cyano; nitro; trihalomethyl and oxo where each p is independently 1 or 2, q is 0-5, r is 0-5, u is 0-5; each X is independently O, S, or N and s is 0 or 1; provided that q + r + u + s + t is less than 6;
Y is selected from the group consisting of O; S; N; --$(C(R_7)_z)_s$—where each R_7 is independently as previously defined for R1, each z is independently 1-2, and s is 1-3; --CH=; --CH=CH--; or Y_1CH_2—where Y_1 is O, N, or S; and the dotted lines are optional double bonds, with the proviso that if the ring including Y is a cyclohexane ring or a heterocyclic 5 member ring said ring is not fully unsaturated, and that if Y is O, N or S, the ring including Y contains at least one said double bond,

said compound further having selective agonist activity at the α2B or α2B/α2C adrenergic receptor subtype(s) over the α2A adrenergic receptor subtype,

~~and~~ or all pharmacologically acceptable salts, esters, stereoisomers or racemic mixtures thereof.

2. ~~4.~~ (Twice Amended) The compound of claim 1 in which the ring including Y has either a single double bond or no double bond, except that when an R_2 and an R_3 together consist of ~~comprise~~ a saturated, unsaturated or partly saturated ring structure said Y-including ring optionally shares an additional double bond with said condensed ring, provided Y is not S, O, or N.

9. ~~11.~~ (Twice Amended) The compound of claim 2, in which each R_2 and each R_3 are independently selected from the group consisting of: H; C_{1-4} alkyl; C_{1-4} alkenyl; C_{1-4} alkynyl; halide; trihalomethyl; cycloalkyl; $(CH_2)_n$-X-$(CH_2)_m$-$(R_5)_o$, where X is O, S or N, n is 0-3, m is 0-3, o is 0-1, and R_5 is methyl or H_{1-2}; or an R_2 and an R_3 together consist of ~~comprise~~ a saturated, partly saturated, or unsaturated ring structure having the formula –$(C(R_6)_p)_q$-X_s-$(C(R_6)_p)_r$ –X_t—$(C(R_6)_p)_u$ where each R_6 is independently selected from the group consisting of H; halogen; C_{1-4} alkyl; C_{1-4} alkenyl; C_{1-4} alkynyl; --COR_4 where R_4 is H, C_{1-4} alkyl or C_{1-4} alkoxy; C_{3-6} cycloalkyl; aryl; heteroaryl; cyano; nitro; trihalomethyl; and oxo where each p is independently 1 or 2, q is 0-4, r is 0-4, u is 0-4; each X is independently O, S, or N, s is 0 or 1, and q + s+ r + t + u = 3 or 4.

1012. (Twice Amended) The compound of claim 3, in which each R_2 and each R_3 are independently selected from the group consisting of: H; C_{1-4} alkyl; C_{1-4} alkenyl; C_{1-4} alkynyl; halide; trihalomethyl; cycloalkyl; $(CH_2)_n$-X-$(CH_2)_m$-$(R_5)_o$, where X is O, S or N, n is 0-3, m is 0-3, o is 0-1, and R_5 is methyl or $H_{1-2;}$ or an R_2 and an R_3 together consist of ~~comprise~~ a saturated, partly saturated, or unsaturated ring structure having the formula –$(C(R_6)_p)_q$-X_s-$(C(R_6)_p)_r$ –X_t—$(C(R_6)_p)_u$ where each R_6 is independently selected from the group consisting of H; halogen; C_{1-4} alkyl; C_{1-4} alkenyl; C_{1-4} alkynyl; --COR_4 where R_4 is H, C_{1-4} alkyl or C_{1-4} alkoxy; C_{3-6} cycloalkyl; aryl; heteroaryl; cyano; nitro; trihalomethyl; and oxo where each p is independently 1 or 2, q is 0-4, r is 0-4, u is 0-4; each X is independently O, S, or N, s is 0 or 1, and q + s+ r + t + u = 3 or 4.

71. (Twice Amended) The compound of claim 53 in which an R_2 and an R_3 together consist of ~~comprise~~ a saturated, partly saturated, or unsaturated ring structure having the formula –$(C(R_6)_p)_q$-X_s-$(C(R_6)_p)_r$ –X_t—$(C(R_6)_p)_u$ where each R_6 is independently selected from the group consisting of H; halogen; C_{1-4} alkyl; C_{1-4} alkenyl; C_{1-4} alkynyl; --COR_4 where R_4 is H, C_{1-4} alkyl or C_{1-4} alkoxy; C_{3-6} cycloalkyl; aryl; heteroaryl; cyano; nitro; trihalomethyl; and oxo where each p is independently 1 or 2, q is 0-4, r is 0-4, u is 0-4; each X is independently O, S, or N, s is 0 or 1, and q + s+ r + t + u = 3 or 4.